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Cross-Metathesis Functionalized Exo-Olefin Derivatives of Lactide

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((Additional Supporting Information may be found in the online version of this article.))

ABSTRACT

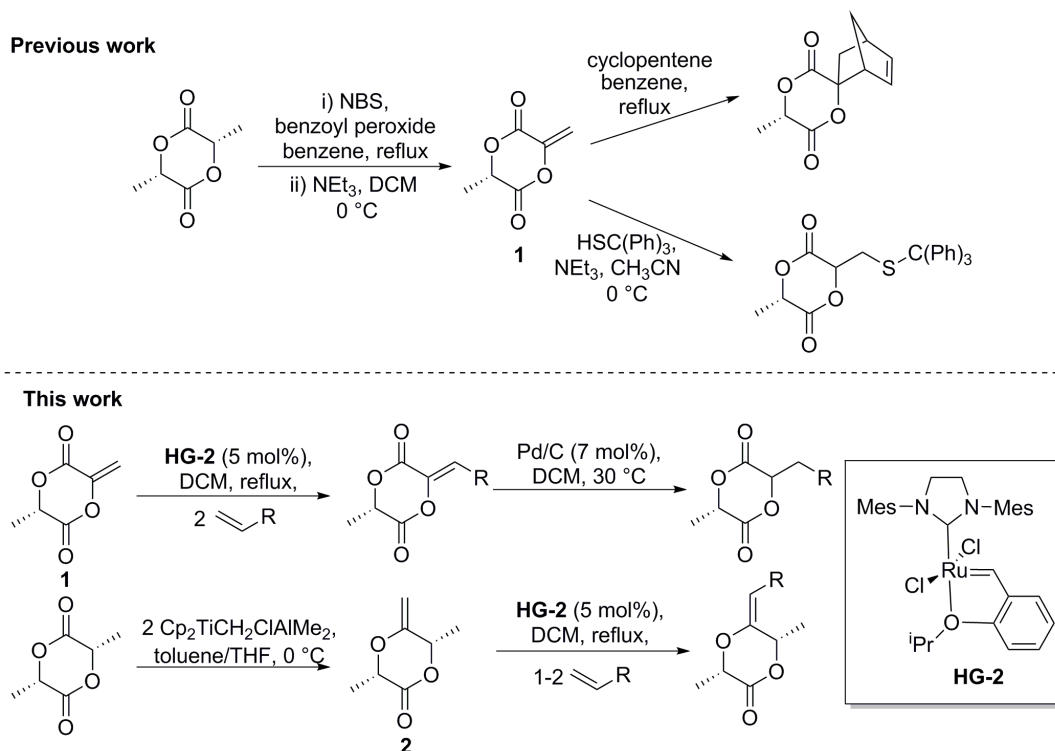
Poly(lactic acid) is at the forefront of research into alternative replacements to fossil fuel derived polymers, yet preparation of derivatives of this key biodegradable polymer remain challenging. This paper explores the use of two derivatives of lactide, each of which features an exocyclic olefin, and their pre-polymerization modification by olefin cross-metathesis. Methylenation of lactide with Tebbe's reagent generates a novel 5-methylenated lactide monomer, (3*S*,6*S*)-3,6-dimethyl-5-methylene-1,4-dioxan-2-one, complementing the previously reported 3-methylenated (6*S*)-3-methylene-6-methyl-1,4-dioxan-2,5-dione. While ring-opening of each monomer is not productive, olefin cross-metathesis can be used to functionalize each of the exocyclic olefins to produce a family of monomers. The ring-opening polymerization of these new monomers, and their hydrogenated congeners, is facilitated by organo- and Lewis-acid catalysts. Together, they offer a new strategy for derivatising and altering the properties of poly(lactic acid).

INTRODUCTION

Poly(lactic acid) (PLA) is a biodegradable and bioassimilable polymer sourced from renewable resources, making it an attractive alternative to petroleum derived plastics.^{1–3} The ring-opening polymerization (ROP) of the inexpensive cyclic diester lactide is straightforward, facilitating the industrial development of homo- and co-polymers with applications in bone fixation, sutures and drug delivery,^{3–5} as well as in drink and fresh food packaging.^{1,6} While PLA has an established commercial prevalence, expanding the properties beyond the shallow current market is more challenging. Research into alternative green feedstocks⁷ is one solution to PLA's limitations. This includes using upcycled CO₂ in copolymerizations with epoxides⁸, synthesis of fatty amide derivatives from plant oils for use as platform chemicals for polymers,⁹ synthesis of a novel bio-based isosorbide derivative for the development of block copolymers¹⁰ and the use of carbohydrates in

the biosynthesis of poly(hydroxyalkanoate).¹¹ Yet, the pursuit to modify the properties of PLA is still an area of current interest, including blending, plasticizer incorporation, surface modification and copolymerization.^{12–17}

While research into these post-polymerization and copolymerization strategies has been extensive, modification of the lactide monomer itself has been limited. Functional derivatives of lactide have been prepared by Baker *et al.* through condensation of substituted α -hydroxy acids,¹⁸ producing polymers with tunable thermal properties.^{19–21} but these did not directly use the inexpensive lactide feedstock. The direct modification of lactide is more challenging: Hillmyer and coworkers synthesized a 3-methylenated lactide, (6*S*)-3-methylene-6-methyl-1,4-dioxan-2,5-dione, (**1**, **SCHEME 1**) from a route previously devised by Scheibelhoffer.^{22,23} The olefin functionality permits Diels Alder coupling²³ and thiol



SCHEME 1 Top: previous work, synthesis of compound **1** and subsequent Diels Alder and thiol addition.¹⁷⁻¹⁹

Bottom: this work using compound **1** for olefin cross- metathesis and hydrogenation and synthesis of compound **2** from the methylenation of lactide using Tebbe's reagent followed by olefin cross-metathesis.

addition²⁴ to give chemically modified poly(lactic acid)s.

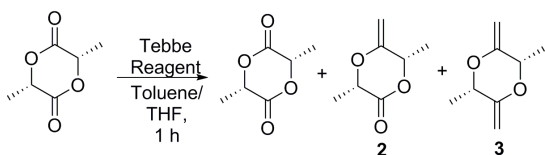
We now report the synthesis of a complementary 5-methyleneated derivative, (3*S*,6*S*)-3,6-dimethyl-5-methylene-1,4-dioxan-2-one, (**2**, **SCHEME 1**) through reaction of lactide with Tebbe's reagent, $\text{Cp}_2\text{TiCH}_2\text{ClAlMe}_2$. For both **1** and **2**, the exocyclic olefin permits a broad range of further functionalization. In this contribution, our focus is on the use of olefin cross-metathesis (CM) to prepare a family of new monomers. Examples of CM in post-polymerization modification in the literature are growing.²⁵⁻³² Most recently, we demonstrated the first successful double metathesis on copolymers of lactide and β -heptenolactone through manipulation of olefin Type reactivity.³³ However, its use in pre-polymerization modification of monomers is scarce.^{34,35} We show that the exocyclic methylenes on the two lactide derivatives (**1** and **2**), can serve as a

platform for modification of these key renewable monomers through CM, but also that reaction conditions must be carefully controlled to prevent decomposition prior to ring-opening.

RESULTS AND DISCUSSION

Methylenation of Lactide

In an effort to more fully explore modification of the lactide monomer, we targeted a novel exocyclic olefin derivative by mono-methylenation with Tebbe's reagent. Reaction of lactide with Tebbe's reagent afforded the desired product, **2**, as well as a di-methylenated derivative, **3**. Careful control of reaction conditions (**TABLE 1**) were essential to optimize yields of **2**, with temperature, Tebbe's reagent concentration, and rate of addition all important factors. Two equivalents of Tebbe's reagent, delivered slowly at 0°C or below, gave best selectivity. Higher Tebbe's reagent equivalents (Entry 9) or temperatures (Entry 11)

TABLE 1 Optimization of reaction conditions for the methylenation of lactide using Tebbe's reagent.

Entry	Equiv. TR	Rate of addn. (ml/min)	Temp (°C)	Resid. LA (%) ^a	Conv. 2 (%) ^a	Conv. 3 (%) ^a
1	1	Inst.t	0	65	35	0
2	2	Inst.t	0	35	50	15
3	1	Inst.	-41	64	34	2
4	2	Inst.	-41	31	55	14
5 ^b	2	Inst.	-41	34	58	8
6	2	0.1	-41	36	56	5
7	2	0.1	-72	54	41	5
8	2	0.1	0	26	60	14
9	3	0.1	0	32	30	38
10 ^c	2	0.1	0	30	49	21
11	2	0.1	R.T	25	17	58

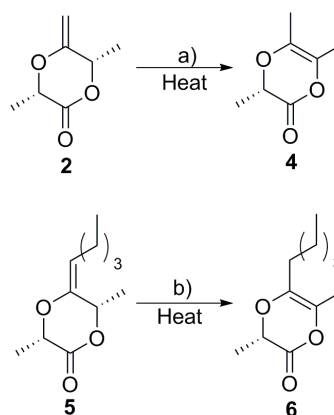
^aDetermined by ¹H NMR spectroscopy monitored by appearance of olefin protons. ^bReaction time increased to 2 h. ^cReaction diluted by 2-fold. Inst.= instantaneous.

avored dimethylenation, while lower temperatures led to high amounts of residual lactide (Entry 7). Purification of **2** was challenging. Isolation by column chromatography suggested inherent stability issues, degrading the monomer into volatile products upon exposure to air. Isolation thus required slow evaporation of the eluent using a stream of nitrogen in an ice bath. The instability of **2** was probed by thermolysis of a sample of isolated **2** in a Young's tap NMR tube. Slow rearrangement of **2** to form **4** (**SCHEME 2**, **FIGURE S1**) was monitored by disappearance of the methylene protons and growth of a new quartet and singlet resonances matching the assignment of endocyclic olefin derivative, **4**. CM of **2** may access monomer derivatives that are more stable and would resist this isomerization. We initially investigated the

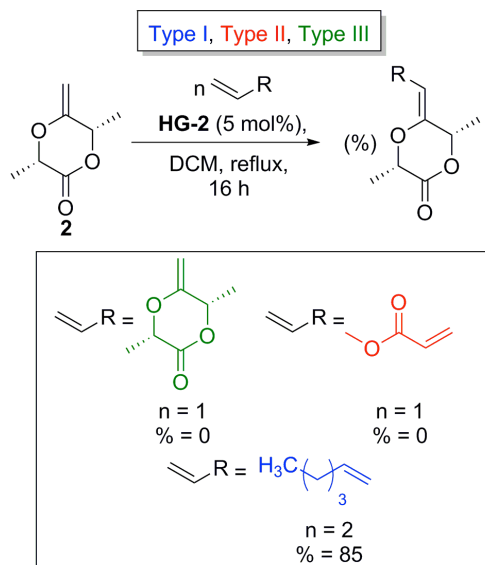
olefin Type of **2** to determine its level of reactivity (**SCHEME 3**). Homodimerization of the monomer gave no reaction; based on Grubbs' model,³⁶ **2** is thus either a Type III olefin (unable to homodimerize, but can react with olefins of a different Type) or a Type IV olefin (inert to metathesis). While reaction with Type II olefin, methyl acrylate, was unsuccessful, reaction with Type I olefin hex-1-ene produced **5** in 85% yield, confirming **2** is a Type III olefin of low reactivity.

Unfortunately, new monomer **5** also showed thermal instability, rearranging to endocyclic olefin **6** (**SCHEME 2**, **FIGURE S2**). However, the transformation was slower than for the unsubstituted monomer and **5** appeared stable at room temperature, as could be stored, in air, for at least two days without evidence for decomposition (**FIGURE S3**).

Despite this improved stability, ROP of both **2** and **5** with organocatalyst TBD or Lewis acids ^tBu[salen]AlMe and Sn(oct)₂ were unproductive (**TABLE S1**). A lower release in ring strain and a less favorable enthalpy of polymerization likely exists for these monomers compared to lactide.



SCHEME 2 Route a) thermal rearrangement of **2** to form **4**; Route b) thermal rearrangement of **5**, formed from the CM of **2** with hex-1-ene, to form **6**.



SCHEME 3 Olefin cross-metathesis of **2** with itself, Type II olefin methyl acrylate and Type I olefin hex-1-ene.

Olefin Cross-Metathesis of **1**

Due to the low stabilities of exocyclic olefin derivatives **2** and **5**, we focused our efforts on the CM of Hillmyer's original exocyclic olefin derivative, **1**. ROP of **1** is also unproductive (**TABLE S2**), instead promoting monomer decomposition. In line with work by Miyake *et al.*³⁷ we confirmed that **1** prefers regio-selective alcoholysis rather than productive ring-opening, with the benzyl alcohol initiator initially serving as the alcohol source. Addition of alternative alcohols generated a family of new small molecule products (**SCHEME S1**).

We again hypothesized CM of **1** may inhibit alcoholysis; as for **2**, monomer **1** was determined to be a low-reactivity Type III olefin. Dec-1-ene was used as a cross-partner for optimizing reaction conditions (**TABLE S3**). A catalyst loading of 5 mol%, 2 equivalents of cross-partner in refluxing dichloromethane gave optimum yields (**TABLE 2**, Entry 2). Using these conditions the substrate scope was expanded to include other Type I olefins: dodec-1-ene, oct-1-ene, and hex-1-ene (Entries 3–5). Functionalized Type I olefins, β -6-heptenolactone and allyl

TABLE 2 Olefin cross-metathesis of **1** with Type I-Type III cross-partners.

Type I, Type II, Type III

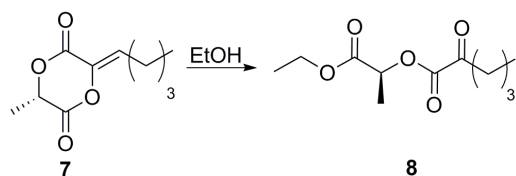
Entry	$\text{R} =$	HG-2 (mol %)	Solvt	Temp (°C)	Time	CP (%) ^a
1 ^b		2	DCM	~45	16 h	0
2		5	DCM	~45	16 h	>99
3		5	DCM	~45	16 h	>99
4		5	DCM	~45	16 h	>99
5		5	DCM	~45	16 h	>99
6		5	DCM	~45	16 h	0
7		5	DCM	~45	2.5 days	0
8		5	DCM	~45	16 h	18
9		10	DCM	~45	7 days	71
10		10	PFT	100	7 days	87
11		5	DCM	50	2.5 days	0
12		5	PFT	100	7 days	0
13		10	Tol	100	7 days	0

^aDetermined by ¹H NMR spectroscopy, monitored by consumption of **1** olefin protons and appearance of cross-product protons. ^bEquivalents of cross partner = 1.

phosphonate, gave no selective CM (Entries 6 and 7), suggesting the highly hindered olefin in **1** requires a suitably unhindered partner. To test this theory, 5-hexenyl acetate was used as a cross partner, producing the desired product (Entry 8), albeit in low yield (18%). Increasing the catalyst loading and reaction time to 10

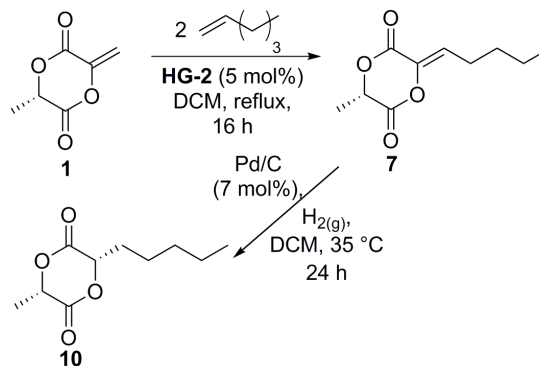
mol% and 7 days respectively significantly increased conversion (71 %, Entry 9). Switching the solvent from DCM to perfluorotoluene (PFT),³³ further increased the conversion to 87 % (Entry 10). As expected from the low reactivity of **1**, switching the cross-partner to Type II olefins was unsuccessful under various conditions (Entries 11-13).

Hydrogenation of **7**



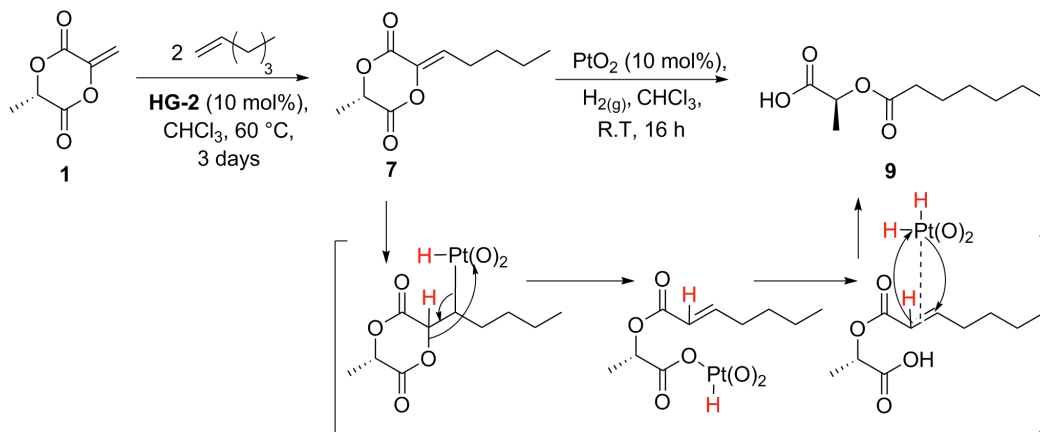
SCHEME 4 Alcoholysis of **7** with ethanol to form compound **8**.

Olefin CM of **1** with hex-1-ene was repeated to form 3-hexenyl lactide **7** (**SCHEME 4**). Purification *via* column chromatography unfortunately promoted monomer decomposition once again. Analysis of degradation products indicated the formation of **8** (**SCHEME 4**). The susceptibility of **1** towards alcoholysis was not eliminated by exo olefin incorporation. The DCM eluent system contained a small amount of ethanol stabilizer, promoting degradation of **7** to **8**. With the knowledge that ROP would mirror the reactivity of **1**, hydrogenation of **7** was pursued to eliminate the olefin moiety. Cossy *et al.*



SCHEME 6 Tandem olefin cross-metathesis/hydrogenation of **1** with hex-1-ene, **HG-2** and Pd/C to form **10**.

reported the formation of substituted lactones in a one-pot tandem CM/hydrogenation reaction using **HG-2** and heterogeneous PtO₂.³⁴ Following from their work a one-pot, one step tandem CM/hydrogenation of **1** was explored, but competing formation of the original lactide monomer occurred. Thus, a one-pot, two-step route was used in monomer synthesis. Interestingly, the analysis of the purified product from the CM/hydrogenation of **1** with hex-1-ene revealed the formation of **9** (Error! Reference source not found.). We hypothesized that during hydrogenation with PtO₂, β-C-O elimination followed by sequential hydrogenation could yield **9**. This is an unusual but unique pathway to synthesize these ring-opened derivatives. Switching the hydrogenation catalyst to Pd/C led to successful hydrogenation without any ring- opening to



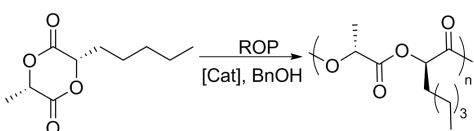
SCHEME 5 Tandem olefin cross-metathesis/hydrogenation of **1** with hex-1-ene, HG-2 and PtO₂ to form compound **9** and hypothesized pathway for β -C-O cleavage.

form 3-hydrogenated hexenyl lactide **10** (**SCHEME 6, FIGURE S4**). ¹H NMR spectroscopy revealed the presence of one major diastereomer (>98 %). Assuming no epimerization of the remaining methine carbon during both metathesis and hydrogenation, 2D nOe NMR spectroscopy suggests the formation of (S,S) 3-hydrogenated hexenyl lactide as the major diastereomer (**FIGURE S5**).

Ring-Opening Polymerization of **10**

ROP of **10** was attempted using three different catalysts; organocatalyst **TBD** and Lewis acids ^tBuPr[salen]AlMe (**Al**) and Sn(oct)₂ (**Sn**) (**TABLE 3**). In contrast to monomer **7**, all catalysts were active polymerization catalysts, confirming hydrogenation had successfully eliminated competing alcoholysis. Although **TBD** was the quickest ROP catalyst, the polymer had a broad dispersity suggesting transesterification (Entry 1). Conversion using both Lewis acid catalysts plateaued at ~90 % (Entries 2 and 3), which could be attributed to the associated increase in steric congestion around the metal centers as the hexyl groups of the growing chains inhibit further coordination/insertion. This is consistent with lower polymer conversions observed by Moller *et al.* with similar functionalized lactide derivatives.³⁵

TABLE 3 Ring-opening polymerization of **10** under various reaction conditions.

							
Entry ^a	Cat.	Solv ^b	Temp (°C)	Time (h)	Conv (%) ^c	\bar{D} ^d	M_n ^d
1	TBD	DCM	R.T	0.25	>99	1.6	6,300
2	Sn	Tol	120	18	92	1.3	9,700
3	Al	Tol	85	24	89	1.4	4,400

^aCatalyst: initiator: monomer 50:1:1. ^bDeuterated solvents.

^cDetermined by ¹H NMR spectroscopy by comparison of monomer to polymer resonance. ^dDetermined by triple detection GPC.

Thermal analysis by DSC of the three polymers (**FIGURE 1**) prepared with the different catalysts showed that **TBD** and ^tBuPr[salen]AlMe produced

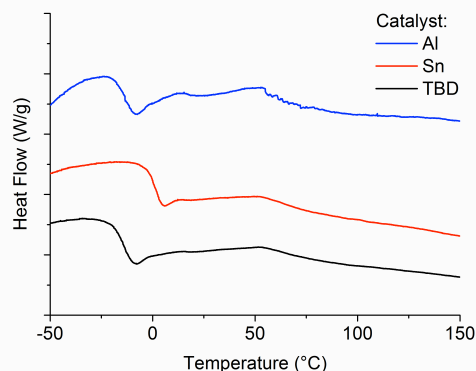


FIGURE 1 DSC of homopolymers of **10** synthesized from catalysts ^tBuPr[salen]AlMe (**Al**), Sn(oct)₂ (**Sn**) and **TBD**.

polymers with similar T_g s of -14 and -13 °C respectively. Sn(Oct)₂ produced a polymer with a higher T_g of 1 °C, belying a strong molecular weight dependence on thermal properties (**TABLE 3**). No T_m is observed, with the flexible hexyl chain inducing more motion compared to the methyl group of lactide, removing order and crystallinity from PLA.

This is one of only a few examples in the literature that demonstrates successful pre-polymerization modification of lactide and to the best of our knowledge is the only report that uses olefin CM to modify lactide followed by successful polymerization.

EXPERIMENTAL

General methods and materials. Experiments involving air- and moisture-sensitive compounds were performed under a nitrogen atmosphere using a Vigor glovebox equipped with a -35 °C freezer and [H₂O] and [O₂] analyzers or using standard Schlenk techniques. Toluene, tetrahydrofuran and dichloromethane were obtained from an Innovative Technologies

solvent purification system incorporating columns of alumina and copper catalysts and prior to use were de-gassed by three freeze-pump-thaw cycles. For a full list of chemicals and materials and complete experimental details, see the Supporting Information.

Characterization. Gel permeation chromatography was performed using a Malvern Instruments Viscotek 270 GPC Max triple detection system with 2 × mixed bed styrene/DVB columns (300 × 7.5 mm) in THF at a flow rate of 1 ML min⁻¹ and an injection volume of 200 μL. Samples for analysis were pre-dissolved in chloroform and known concentrations were inputted into the software for molecular weight determination. ¹H NMR spectra were recorded at 298 K using BrukerAvance spectrometers (400, 500 or 600 MHz). ¹³C NMR spectra were recorded using BrukerAvance spectrometers (126 MHz). Differential scanning calorimetry was carried out using TA instruments DSC 2500 through a heat/cool/heat cycle between -90 °C and 200 °C at a rate of 10 °C min⁻¹. Cooling baths at 0, -41, and -72 °C were prepared using ice, dry ice/acetonitrile, and dry ice/ethanol respectively. Mass spectra (EI/ESI) were recorded using Bruker MicroTof II spectrometer.

Representative methylenation of lactide to form 2 and 3. In a glovebox L-lactide (0.85 g, 5.897 mmol) was dissolved in THF (17 mL) and charged to an ampoule. In a second ampoule, Tebbe's reagent (3.360 g, 11.794 mmol) was dissolved in toluene (68 mL). Outside the box, both solutions were cooled to 0 °C and the reagent solution was added dropwise to the solution of lactide *via* cannula under a nitrogen atmosphere. The reaction was then left to stir for 1 h. The solution was subsequently diluted with diethyl ether, filtered through Celite, extracted with diethyl ether and concentrated *in vacuo* to yield an orange oil. The product was purified via column chromatography on silica gel (petroleum ether:ethyl acetate, 85:15). Evaporation of the combined fractions was

carried out at 0 °C in an ice bath using a stream of nitrogen to afford **2**, **3** and residual lactide. **2**: 18% yield. ¹H NMR (500 MHz, CDCl₃, δ): δ 5.06 (qd, J = 6.4 Hz, 1 Hz, 1H, H_aH_b=CCH), 4.70 (q, 6.5 Hz, 1H, O=CCH), 4.52 (dd, J = 2.3 Hz, 1 Hz, 1H H_aH_b=C), 4.25 (m, 1H, H_aH_b=C), 1.59 (d, J = 6.4 Hz, 3H, H_aH_b=CCCH₃), 1.57 (d, J = 6.5 Hz, 3H, O=CCCH₃). ¹³C NMR {1H} (CDCl₃, δ): 170.4, 155.4, 87.4, 71.9, 69.9, 17.0, 16.0. HRMS (ESI, m/z): [M + H]⁺ calcd for C₇H₁₀O₄, 143.0703; found, 143.0713. **3**: negligible yield. ¹H NMR (500 MHz, CDCl₃, δ): 4.80 (qd, J = 6.3 Hz, 1 Hz, 2H, H_aH_b=CCH), 4.34 (dd, 2.0 Hz, 1.0 Hz, 2H, H_aH_b=C), 4.05 (m, 2H, H_aH_b=C), 1.45 (d, J = 6.3 Hz, 6H, H_aH_b=CCCH₃). ¹³C NMR {1H} (126 MHz, CDCl₃, δ): 159.4, 84.71, 68.1, 17.2. HRMS (ESI, m/z): [M + H]⁺ calcd for C₈H₁₂O₂, 141.0910; found, 141.0913.

Representative olefin cross-metathesis of 2 to form 5. In a glovebox, in a glass ampoule, **2** (0.060 g, 0.422 mmol), hex-1-ene (0.106 g, 0.282 mmol) and Hoveyda-Grubbs Second Generation catalyst (0.013 g, 0.021 mmol) were dissolved in DCM (3 mL). The ampoule was sealed and brought outside the box, where the solution was de-gassed by one freeze-pump-thaw cycle and subsequently heated at reflux for 16 h. The solvent was then evaporated using a stream of nitrogen at 0 °C in an ice bath. The crude product was purified *via* column chromatography on silica gel (petroleum spirits:ethyl acetate, 70:30). Evaporation of the combined fractions was carried out at 0 °C in an ice bath using a stream of nitrogen to afford **5** as a colorless oil, 30 % yield. ¹H NMR (500 MHz, CDCl₃, δ): 5.05 (m, 1H, RHC=CCH), 4.68 (q, 6.6 Hz, 1H, O=CCH), 4.65 (m, 1H, RHC=C), 2.08-2.14 (m, 2H, CH₂(CH₂)₂CH₃), 1.57 (d, 6.6 Hz, 3H, O=CCCH₃), 1.54 (d, 6.3 Hz, 3H, RHC=CCCH₃), 1.38-1.33 (m, 4H, CH₂(CH₂)₂CH₃), 0.92 (m, 3H, CH₂(CH₂)₂CH₃). ¹³C NMR {1H} (126 MHz, CDCl₃, δ): 170.8, 147.2, 105.0, 72.7, 70.1, 31.5, 22.3, 23.7, 17.1, 16.4, 13.9. HRMS (ESI m/z): [M + H]⁺ calcd for C₁₁H₁₈O₃, 199.1329; m/z found, 199.1322.

NMR degradation of 2 and 5 to form 4 and 6. In two separate Young's tap NMR tubes, **2** and **5** were dissolved in CDCl_3 and placed in a pre-heated oil bath at 60 °C. Degradation with time was monitored over 6 days by ^1H NMR spectroscopy. The temperature was increased gradually over this period, reaching a maximum of 105 °C. **4**: ^1H NMR (500 MHz, CDCl_3 , δ): 4.32 (q, J = 6.7 Hz, 1H, $\text{O}=\text{CCH}$), 1.92 (q, J = 1.1 Hz, 3H, $\text{O}=\text{COCCH}_3$), 1.83 (q, J = 1.1 Hz, 3H, CHOCCH_3), 1.56 (d, J = 6.7 Hz, 3H, $\text{O}=\text{CCCH}_3$). ^{13}C NMR $\{^1\text{H}\}$ (126 MHz, CDCl_3 , δ): 166.5, 132.2, 129.1, 70.4, 15.6, 14.3, 14.1. HRMS (ESI m/z): $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_7\text{H}_{10}\text{O}_3$, 165.0522; found, 165.0536. **6**: ^1H NMR (500 MHz, CDCl_3 , δ): 4.29 (q, J = 6.8 Hz, 1H, $\text{O}=\text{CCH}$), 2.14–2.11 (m, 2H, $\text{CH}_2\text{CH}_2(\text{CH}_2)_2\text{CH}_3$), 1.92 (s, 3H, $\text{O}=\text{COCCH}_3$), 1.55 (d, 6.8 Hz, 3H, $\text{O}=\text{CCCH}_3$), 1.53–1.50 (m, 2H, $\text{CH}_2\text{CH}_2(\text{CH}_2)_2\text{CH}_3$), 1.34–1.31 (m, 4H, $\text{CH}_2\text{CH}_2(\text{CH}_2)_2\text{CH}_3$), 0.92 (m, 3H, $\text{CH}_2\text{CH}_2(\text{CH}_2)_2\text{CH}_3$). ^{13}C NMR $\{^1\text{H}\}$ (126 MHz, CDCl_3 , δ): 166.6, 135.8, 129.3, 70.5, 31.3, 28.5, 26.6, 22.4, 15.6, 14.0, 14.0. HRMS (ESI, m/z): $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{11}\text{H}_{18}\text{O}_3$, 221.1148; found, 221.1154.

Representative ring-opening polymerization of 2 and 5. In a glovebox to an ampoule **5** (0.025 g, 0.126 mmol), TBD (0.6 mg, 4.206 $\times 10^{-3}$ mmol) and BnOH (0.4 μL , 4.206 $\times 10^{-3}$ mmol) were dissolved in dichloromethane- d_2 (0.6 mL). Outside the box the reaction was left at room temperature for 24 h and quenched with methanol. The same molar ratio of reagents was used as above for catalyst $\text{Sn}(\text{Oct})_2$ for 24 h at 120 °C. **2** used catalyst $^t\text{BuPr}[\text{salen}]\text{AlMe}$ for 24 h at 85 °C. Polymerizations were unsuccessful as determined by ^1H NMR spectroscopy.

Representative olefin cross-metathesis of 1 to form 7 and then purification to form 8. In a glovebox to an ampoule **1** (0.02 g, 0.140 mmol), hex-1-ene (0.024 g, 0.282 mmol) and Hoveyda-Grubbs Second Generation catalyst (0.0044 g, 7 $\times 10^{-3}$ mmol) were dissolved in DCM (1 mL). Outside the box the ampoule was de-gassed by one freeze-pump-thaw cycle and heated at reflux for 16 h. The reaction was cooled to room

temperature and analysed *via* ^1H NMR spectroscopy. **7**: ^1H NMR (500 MHz, CDCl_3 , δ): 6.45 (t, J = 7.9 Hz, 1H, $\text{C}=\text{CH}$), 4.99 (q, J = 7.0 Hz, 1H, $\text{O}=\text{CCH}$), 2.39–2.35 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.72 (d, J = 7.0 Hz, 3H, $\text{O}=\text{CCCH}_3$), 1.52–1.47 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.42–1.31 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.95 (t, 7.3 Hz, 3H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$). ^{13}C NMR $\{^1\text{H}\}$ (CDCl_3 , δ): 163.5, 158.6, 136.8, 129.8, 72.0, 30.1, 25.0, 22.3, 17.2, 13.7. Purification of **7** (petroleum spirits then DCM (stabilized with 0.2 % ethanol)) formed **8**: ^1H NMR (500 MHz, CDCl_3 , δ): 5.17 (q, J = 7.1 Hz, 1H, CHCH_3), 4.23 (q, J = 7.2 Hz, 2H, CH_3CH_2), 2.87–2.81 (m, 2H, $\text{O}=\text{CCH}_2$), 1.69–1.63 (m, 2H, $\text{CH}_2(\text{CH}_2)_2\text{CH}_3$), 1.59 (d, J = 7.1 Hz, 3H, CHCH_3), 1.36–1.31 (m, 4H, $\text{CH}_2(\text{CH}_2)_2\text{CH}_3$), 1.28 (t, J = 7.2 Hz, 3H, CH_3CH_2), 0.9–0.88 (m, 3H, $\text{CH}_2(\text{CH}_2)_2\text{CH}_3$). ^{13}C NMR $\{^1\text{H}\}$ (126 MHz, CDCl_3 , δ): 193.9, 169.6, 160.5, 70.2, 61.8, 30.4, 31.1, 22.6, 22.3, 14.1, 13.8. HRMS (ESI m/z): $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{12}\text{H}_{20}\text{O}_5$, 267.1203; found, 267.1191.

Representative tandem olefin cross-metathesis and hydrogenation of 1. Using PtO_2 : In a glove box to an ampoule **1** (0.5 g, 3.518 mmol), dec-1-ene (0.998 g, 7.036 mmol), and Hoveyda Grubbs Second Generation catalyst (0.11g, 0.176 mmol) were dissolved in DCM (15 mL). Outside the box the ampoule was de-gassed by one freeze-pump-thaw cycle and heated at reflux for 16 h. A crude NMR was taken, then PtO_2 (0.048 g, 0.176 mmol) was added to the ampoule which was then de-gassed by three freeze-pump-thaw cycles. Hydrogen gas (1 bar, 14 psi) was then introduced into the vessel and stirred at room temperature for 24 h. The product was purified *via* column chromatography on silica gel (flushed with petroleum spirits followed by ethyl acetate) to yield the ring-opened product **9** from β -elimination during the hydrogenation (>99 % by NMR). ^1H NMR (500 MHz, CDCl_3 , δ): 5.16 (q, J = 7.1 Hz, 1H, CHCH_3), 2.43–2.38 (m, 2H, $\text{CH}_2\text{CH}_2(\text{CH}_2)_3\text{CH}_3$), 1.68 (p, J = 7.5 Hz, 2H, $\text{CH}_2\text{CH}_2(\text{CH}_2)_3\text{CH}_3$), 1.56 (d, J = 7.1 Hz, 3H, CHCH_3), 1.42–1.30 (m, 6H, $\text{CH}_2\text{CH}_2(\text{CH}_2)_3\text{CH}_3$), 0.91 (t, J = 6.9 Hz, 3H, $\text{CH}_2\text{CH}_2(\text{CH}_2)_3\text{CH}_3$). ^{13}C NMR $\{^1\text{H}\}$ (126 MHz, CDCl_3 , δ): 173.8, 173.3, 67.8, 33.9, 31.4, 28.8, 24.7, 22.5, 16.1, 14.0,

HRMS (ESI, m/z): $[M + Na]^+$ calcd for $C_{10}H_{18}O_4$, 225.1097; found, 225.1089. **Using Pd/C:** The same procedure was used as above with replacement of PtO_2 with Pd/C and the hydrogenation was carried out at 35 °C. The product was filtered through celite to remove Pd/C and purified *via* column chromatography on silica gel (petroleum spirits: ethyl acetate, 70:30) to afford **10**, a white solid, 42% yield. 1H NMR (500 MHz, $CDCl_3$, δ): 5.02 (q, $J = 6.7$ Hz, 1H, $CHCH_3$), 4.9 (dd, $J = 7.7$ Hz, 4.3 Hz, 1H, $OCHCH_aH_b$), 2.13 (dddd, $J = 14.8$ Hz, 10.4 Hz, 5.9 Hz, 4.3 Hz, 1H, $OCHCH_aH_b$), 1.98 (dddd, $J = 14.8$ Hz, 10.4 Hz, 7.7 Hz, 4.9 Hz, 1H, $OCHCH_aH_b$), 1.7 (d, $J = 6.7$ Hz, 3H, $CHCH_3$), 1.6–1.52 (m, 2H, $CH_2(CH_2)_2CH_3$), 1.37–1.38 (m, 4H, $CH_2(CH_2)_2CH_3$), 0.93–0.88 (m, 3H, $CH_2(CH_2)_2CH_3$). ^{13}C NMR $\{^1H\}$ (126 MHz, $CDCl_3$, δ): δ 167.8, 167.4, 75.9, 72.3, 31.2, 30.0, 24.0, 22.3, 13.9, 15.9. NOSEY analysis shows coupling in space between protons δ 5.02 and δ 4.90 indicating a cis-relationship. HRMS (ESI, m/z): $[M + Na]^+$ calcd for $C_{10}H_{16}O_4$ 223.0940; found, 223.0933.

Representative ring-opening polymerization of **10**.

In a glove box to a Young's tap NMR tube **10** (0.08 g, 0.398 mmol), TBD (0.0011 g, 7.96×10^{-3} mmol) and BnOH (0.8 μ L, 7.96×10^{-3} mmol) were dissolved in dichloromethane- d_2 (0.8 mL). Outside the box the reaction was monitored by 1H NMR and quenched after 0.25 h with benzoic acid (0.003 g). The polymer was precipitated to yield an oil. The same molar ratio of reagents was used as above for the following catalysts; $Sn(oct)_2$ at 120 °C for 18 h and $^{tBu}Pr[Salen]AlMe$ at 85 °C for 24 h. 1H NMR (500 MHz, $CDCl_3$, δ): 5.20 (br, 1H, $CHCH_3$), 5.09 (br, 1H, $CHCH_aH_b(CH_2)_3CH_3$), 1.97 (br, 1H, $CH(CH_aH_b(CH_2)_3CH_3)$), 1.90 (br, 1H, $CH(CH_aH_b(CH_2)_3CH_3)$), 1.56 (br, 3H, $CHCH_3$), 1.46 (br, 2H, $CH_aH_bCH_2(CH_2)_2CH_3$), 1.31–1.32 (br, 4H, $CH_aH_bCH_2(CH_2)_2CH_3$), 0.9 (br, 3H, $CH_aH_bCH_2(CH_2)_2CH_3$). ^{13}C NMR $\{^1H\}$ (126 MHz, $CDCl_3$, δ): 169.3, 169.1, 72.7, 69.0, 31.2, 30.8, 24.6, 22.3, 16.8, 13.9.

CONCLUSIONS

In summary, we have used Tebbe's reagent to successfully synthesize a novel exocyclic olefin derivative of lactide, **2**. The ring can be functionalized by CM with Type I olefins such as hex-1-ene. A second exocyclic olefin derivative of lactide, **1**, can be similarly functionalized pre-polymerization using CM with a range of aliphatic straight chain olefins. Alcoholysis of the functionalized monomers prevents productive polymerization. Attempts to circumvent this through selective olefin hydrogenation with PtO_2 favored an unusual β -C-O bond cleavage over hydrogenation. Along with the aforementioned alcoholysis, an array of ring-opened derivatives are accessible. Hydrogenation using Pd/C catalyst generated a saturated monomer capable of undergoing ROP. Thermal analysis of the resultant polymers displayed the desired low T_g s. This report discloses the challenges of pre-polymerisation modification of the lactide monomer, while showcasing a rare example of olefin CM in monomer synthesis. The work has paved the route to generate an array of functionalised poly(lactic acids). Our current efforts focus on expanding the polymerization to the other functionalized lactide derivatives discussed in this paper for the generation of both homo- and co-polymers with lactide. Furthermore, other pre-polymerisation reactions of **2** are under investigation.

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GRAPHICAL ABSTRACT

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Cross-Metathesis Functionalized Exo-Olefin Derivatives of Lactide

Poly(lactic acid) is a sustainable alternative to many petroleum derived polymers, but chemical modification of its parent monomer lactide is challenging. This article details the synthesis and reactivity of two exocyclic olefin derivatives of the lactide monomer, detailing its sensitivity to various non-productive ring-opening reactions. The paper also showcases the use of olefin cross-metathesis as a tool to functionalize these lactide derivatives, including preparation of asymmetric diesters that can be polymerized to prepare aliphatic polyesters with modified thermal properties.

